REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. Withdrawn Rejection

Applicants acknowledge withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

II. Rejection of Claims Under 35 U.S.C. 103(a)

The rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Yaksh et al. (U.S. Patent No. 6,180,716; hereafter referred to as the '716 patent) and Heywood et al. (1988), and further in view of *Drug Facts and Comparisons* (1994) has been maintained. The Examiner has suggested that the '716 patent teaches that spinal (intrathecal/epidural) administration of centrally acting agents, such as anti-neoplastics and analgesics, have considerable therapeutic efficacy for treatment of pain, spasticity, central nervous system tumors, and infections, and further that methotrexate is one of these centrally acting agents that is given by intrathecal infusion. The Examiner further suggests that Heywood et al. (1998) teach

that rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy while *Drug Facts and Comparisons* (1994) teach administration of methotrexate for rheumatoid arthritis by ameliorating symptoms of inflammation (pain, swelling, stiffness) at doses of from 7.5 mg/week to 15 mg/week. The Examiner acknowledges that the references either alone or combined fail to teach a dose of methotrexate intrathecally of 1 mg/kg every other day for up to 4 days. As a result, the Examiner suggests it would have *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to administer methotrexate intrathecally at the doses claimed (1 mg/kg every other day for up to 4 days) for treatment of lower back pain with radiculopathy because motivation is provided by the teaching of the '716 patent (teaching methotrexate intrathecally) and Heywood et al. (1988; teaching rheumatoid arthritis causes cervical spine instability and is a causative factor in symptoms of radiculopathy) combined with the teaching of *Drug Facts and Comparisons* (1994; teaching that methotrexate is routinely used to treat rheumatoid arthritis to ameliorate symptoms of inflammation at doses of from 7 to 15 mg/week). Further, the Examiner suggests that in terms of the dose cited in the claim, *Drug Facts and Comparisons* teaches that

administration of methotrexate at a dose of 7.5 mg/week could readily be extrapolated by one of skill to an intrathecal dosage to fit the limitation of an animal. The Examiner's rejection is essentially the same as the rejection presented in the Office Action dated February 8, 2010. In response to the arguments presented in the Reply dated May 5, 2010, the Examiner states that although Applicants have exemplified a rat in the specification as filed, the claims are not limited to such, nor are the claims limited to humans. The Examiner further suggests that it is within the routine skill of one in the art "to adjust the dosage to effect a therapeutic result". The Examiner also suggests that since the prior art disclosed that radiculopathy is frequently a concurrent symptom of rheumatoid arthritis and the problem can be addressed by use of methotrexate, and that intrathecal administration of methotrexate was well known, then the dosage of methotrexate by this route is within the routine skill of one in the art, where "nothing unexpected has been demonstrated by administering 1 mg/kg of methotrexate every other day for 4 days". Applicants respectfully disagree with the Examiner's conclusions regarding the combination of cited references.

The particular area with which Applicants disagree relates to the obviousness of the specific dose and dosing interval for intrathecal dosing of methotrexate as claimed in instant claim 1. In claim 1 as amended, the claim recites a very specific limitation for the method which is "consisting of locally administering methotrexate intrathecally into the spinal cord but not the brain of said animal at a dose level of 1 mg/kg every other day for up to 4 days" [emphasis added]. As underlined in the claim language in the previous sentence, there are three very specific limitations that are at issue in the obviousness rejection. In order to establish a *prima facie* case of obviousness, however, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. In instant claim 1, Applicants believe that the cited references, either alone or combined, fail to teach or suggest all claim limitations, specifically the limitations of the methotrexate dose (1 mg/kg), the duration of methotrexate dosing (up to 4 days), and the

interval between methotrexate doses (every other day), where each of these limitations are then applied to intrathecal administration of methotrexate.

The claim recites a "1 mg/kg" dose is administered intrathecally "every other day for up to 4 days". Nowhere in the references cited by the Examiner is such a dose and dosing frequency taught or suggested. As discussed in the previous reply dated May 5, 2010, the only reference that even mentions dosage of methotrexate is limited to oral dosing amounts in humans (see page 1244 of *Drug Facts and Comparisons* 1994). There, the dosage taught is either a single oral dose of 12 mg/week, or a divided oral dose of 2.5 mg at 12 hour intervals for 3 doses given over the course of a week (7.5 mg). This dose level and dosing interval in particular are very different from what is claimed, which specifies dosing only every other day for up to 4 days. If one wanted to extrapolate this dose to something other than a human, such as the rat taught in the specification as filed, using the rat body weight, this is an oral dose of from 60 mg/kg/week for a rat (12 mg x 1/0.2 kg bw for a rat) to 12.5 mg/kg/12 hours (2.5 mg x 1/0.2 kg bw of rat). In the case of methotrexate, a highly toxic drug (see discussion in *Drug Facts and Comparisons* 1994), one of skill in the art

would not be able to extrapolate an oral dose range to an intrathecal dose range, especially going higher in dose, which would occur based on the dosing regimen claimed. These statements made by Applicants are in fact grounded in basic principles of pharmacology and toxicology and have apparently been ignored by the Examiner, but in fact would not be ignored by one of skill in the art.

The most important basic principle that cannot be ignored is the principle of dosing interval and how dosing interval affects drug efficacy. In the instant claim, the dosing interval recited is "once every other day for up to 4 days". As discussed in basic textbooks of pharmacology, drug effectiveness is directly related to the presence of a drug in tissues or blood. If a drug is no longer detected at the site of action for efficacy, then drug effectiveness diminishes or disappears in most cases, requiring that a drug would be administered again (Buxton, I.L.O. 2006. Pharmacokinetics and pharmacodynamics: the dynamics of drug *absorption, distribution, action and elimination. In: Goodman & Gilman's the Pharmacological Basis of Therapeutics, 11th edition.* Brunton, L.L. (editor). McGraw-Hill: New York. Chapter 1: General principles, pp. 1-39). In the case of methotrexate, the oral dose of the drug is taught in the references cited by the Examiner,

although no specific intrathecal dose of methotrexate is taught, and no information is provided at all on the relationship of dose level to tissue or blood levels. Regardless of the route of dosing, however, it is also a general principle of pharmacology that some concentration of methotrexate must be found in tissues or blood in order for the drug to have efficacy (Buxton, I.L.O. 2006. Pharmacokinetics and pharmacodynamics: the dynamics of drug *absorption, distribution, action and elimination. In: Goodman & Gilman's the Pharmacological Basis of Therapeutics, 11th edition.* Brunton, L.L. (editor). McGraw-Hill: New York. Chapter 1: General principles, pp. 1-39). The concentration of methotrexate in blood and tissues, at least, is known to be stipulated by its pharmacokinetic parameter referred to as elimination half-life. The elimination half-life of methotrexate following intrathecal dosing is not reported in the published medical literature. The elimination half-life is the time required for elimination of 50% of the drug from the body. After 5 half-lives, the levels in blood are reduced to less than 10% of the administered dose, amounts that are not usually considered to be pharmacologically active. The elimination half-life of methotrexate after either oral or intravenous dosing is stated to be about 7 hours (see page 1848 of *Goodman & Gilman's the Pharmacological Basis of*

Therapeutics, 11th edition. Brunton, L.L. (editor). McGraw-Hill: New York). Based on this value, 7 hours, in less than 2 days, and likely within one day, there would be no pharmacologically active levels of the drug present in tissues such as the spinal cord. Based on this, one of skill in the art would not expect that every other day dosing was sufficient to treat a condition such as pain or radiculopathy where there is no evidence in the literature cited by the Examiner that efficacy would be expected if blood levels no longer were in the range of pharmacologically active levels. It is only with the specification in hand that one of skill would have evidence and data to show that dosing intrathecally once every other day for up to 4 days was a dosing regimen, a level and an interval, that were sufficient for producing pharmacological effects of methotrexate. Therefore, the combination of prior art references cited by the Examiner fails to teach or suggest each and every limitation of the claims as filed and cannot make obvious the invention of claim 1.

Moreover, a *prima facie* case of obviousness is established only when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). Thus, an obviousness analysis requires

that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). In the instant case, the statements made by the Examiner amount to no more than convenient assumptions about what would have been obvious to the skilled artisan at the time of the invention, without any evidence provided that would refute the general principles of pharmacology upon which one of skill would be forced to rely in order to adjust a dosing regimen of the prior art. However, under MPEP §2144.03, it is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697. See also *In re Thrift*, 298 F.3d 1357, 1364, 63 USPQ2d 2002-2006 (Fed. Cir. 2002)(quoting Lee, 277 F.3d at 1344-45, 61 USPQ2d at 1435) (reliance on "common knowledge and common sense" do not fulfill the requirement to provide reasons in support of the findings of obviousness"). As a result, the Examiner's suggestion that it was *prima facie* obvious because all the claimed elements were known in the prior art is improper. Nowhere does this combination of prior art references provide one of skill with any working

example of using methotrexate intrathecally for treatment of pain with radiculopathy at any dose or dosing interval, including the dose claimed, and the frequency claimed. Accordingly, this combination of prior art references cannot establish a *prima facie* case of obviousness and withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata

Jane Massey Licata
Registration No. 32,257

Date: October 18, 2010

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053
856-810-1515
Email: jmlicata@licataandtyrrell.com